PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
Peggy Wingard et al.	:	Confirmation Number: 2806
Application No. 10/509,627	:	Group Art Unit: 4133
Filed: April 29, 2005	:	Examiner: Sutton, Darryl C.
For: PHARMACEUTICAL COMPOSITIONS CONTAINING WATER-SOLUBLE PRODRUGS OF PROPOFOL AND METHODS OF ADMINISTERING SAME	:	Atty Docket: 006050.00067

DECLARATION OF AJIT SHAH, PH.D. UNDER 37 C.F.R. § 1.132

Commissioner of Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

I, Ajit Shah, Ph.D., declare as follows:

1. I am a pharmacokineticist for Eisai Research Institute. In 2008, Eisai Co., Ltd. acquired MGI Pharma, Inc. and its subsidiary MGI GP, Inc., the current assignee of the above-captioned application. My *curriculum vitae* is attached.

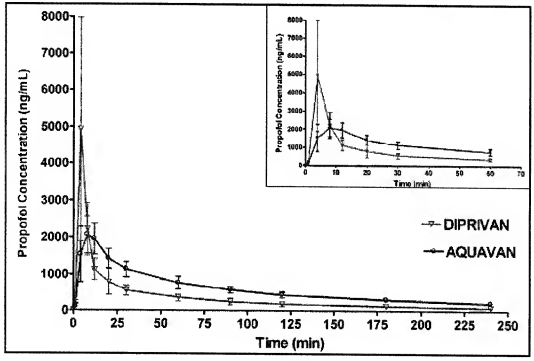
2. I have reviewed the Final Office Action dated September 16, 2008. The Final Office Action asserts that dosages of the prodrug of Formula I effective for producing a conscious sedated state could have been determined from Lowrie et al., "The Pediatric Sedation Unit: A Mechanism for Pediatric Sedation," which describes administering propofol. This assertion is incorrect for reasons I will discuss below.

3. With respect to the Final Office Action's comments concerning Examples 1 and 2 in the present application, I note that the target controlled infusion (TCI) technique described in these examples mimics a fast bolus injection, and may be used for the purpose of achieving the same maximal electroencephalogram (EEG) effect ("BIS" scores).

4. O-phosphonooxymethyl propofol disodium salt (also sometimes referred to as fospropofol disodium) differs from propofol in terms of release kinetics due to hydrolysis by alkaline phosphatase enzymes. As part of extensive clinical pharmacology studies in which I participated, significant differences in plasma concentration-time profiles were observed between propofol and fospropofol disodium. Because of these differences, methods of administering fospropofol disodium for achieving conscious sedation could not have be predicted from data based on propofol.

5. Figure 6 below compares a bolus injection of fospropofol disodium ("Aquavan") with propofol ("Diprivan") injectable emulsion. Figure 6 shows the mean (±SD) propofol concentrations versus time following bolus doses of 10 mg/kg of fospropofol disodium injection or propofol injectable emulsion 50 mg/minute over 2.1 to 4.6 minutes. Subjects received bolus doses of 10 mg/kg of fospropofol disodium injection and after a washout period of 7 days, were infused with propofol injectable emulsion at 50 mg/minute. Propofol concentrations in the plasma from fospropofol disodium had a lower maximum propofol concentration (C_{max}) occurring at a later time (T_{max}) as compared with propofol injection. Also, the decrease in C_{max} in propofol from fospropofol disodium is more gradual as compared to decrease from C_{max} from injection of propofol itself.

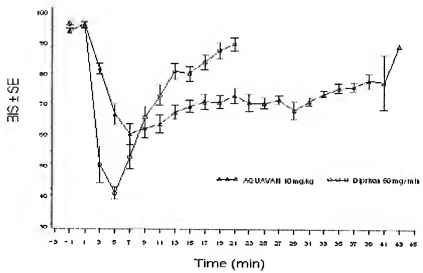
Figure 6: Mean (±SD) Propofol Plasma Concentration Profiles for AQUAVAN 10 mg/kg and DIPRIVAN 50 mg/minute (Study 3000-0625)



6. Figure 7 below shows mean BIS Index and mean MOAA/S score over time following treatment with 10 mg/kg of fospropofol disodium injection and 50 mg/minute infusion of propofol injectable emulsion. Infusion continued until patients reached same minimum BIS as they had previously with the 10 mg/kg fospropofol disodium injection dose. BIS continued to decline as the full propofol effect was reached. Subjects treated with fospropofol disodium injection reached a mean minimum BIS score of 54.0 (range: 40-69) at a mean of 8.2 (range: 5-17) minutes following study drug administration. Subjects treated with propofol injectable emulsion reached a mean minimum BIS score of 37.7 (range: 25-51) at a mean of 4.7 (range: 3-7) minutes after receiving drug. As can be seen from Figure 7, subjects receiving propofol injection experienced deeper sedation than those receiving fospropofol disodium. Recovery

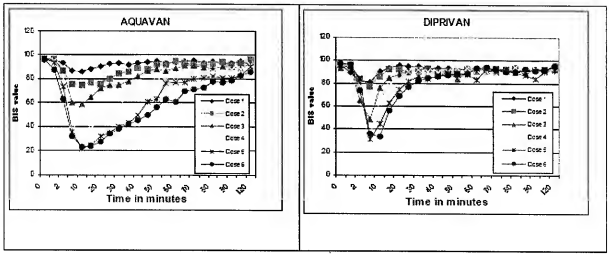
from sedation from propofol derived from fospropofol disodium (green line) was much more gradual than that from the propofol injection (red line). These data show the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of propofol and fospropofol disodium are quite different. In particular, fospropofol disodium provides a slightly slower time to peak effect, achieves a lower peak effect, but provides a more sustained effect, than does administration of propofol injection.

Figure 7: **Mean (±SE) BIS Index Following Treatment of Healthy Subjects with AQUAVAN 10 mg/kg or DIPRIVAN 50 mg/minute (Study 3000-0625)**



7. Figure 11 compares different doses of fospropofol disodium and propofol injection, measuring sedation by BIS score (as in Figure 7 above). Doses were titrated to produce equal overall effects. The data again show that fospropofol disodium produces a slower time to maximum effect, and a more gradual recovery from sedation.

Figure 11 Mean Bispectral Index over Time after Administration of Fospropofol Disodium Injection (AQUAVAN) or Propofol Injectable Emulsion (DIPRIVAN) (Study 3000-0103)



All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 28-Jan-2009

Ajit Shah